414 Rec'd PCT/PTO 07 NOV 2000

FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
2727-127	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	
09/674877	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03159	**07 May 1999 (07.05.99)**	**08 May 1998 (08.05.98)**

TITLE OF INVENTION

"Epothilon Derivatives, Processes for Their Production and Their Use"

APPLICANT(S) FOR DO/EO/US

Gerhard Hoefle, Thomas Leibold

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

WIPO Publication Cover Page

Declaration (unsigned)

PCTUS1/REV03

Express Mail No. EK839442788US

U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR 1.5) 09/674877	INTERNATIONAL APPLICATION NO. PCT/EP99/03159	ATTORNEY'S DOCKET NUMBER 2727-127

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$970.00**
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	**$840.00**
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$690.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$670.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	**$96.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	17 - 20 =	0	x $18.00	**$0.00**	
Independent claims	2 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
	TOTAL OF ABOVE CALCULATIONS =			**$860.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐				**$0.00**	
	SUBTOTAL =			**$860.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 +				**$0.00**	
	TOTAL NATIONAL FEE =			**$860.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
	TOTAL FEES ENCLOSED =			**$860.00**	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account **501145** in the amount of **$860.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **501145** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Ronald R. Santucci
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711 Third Avenue, 20th Floor
New York, New York 10017

(212)687-6000

SIGNATURE

Ronald R. Santucci
NAME

28,988
REGISTRATION NUMBER

November 7, 2000
DATE

2727-127

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (US/DO/EO)

Applicants: Gerhard Hoefle and Thomas Leibold

International Appln. No.: PCT/EP99/03159

International Filing Date: 07 May 1999

Priority Date Claimed: 08 May 1998

For: EPOTHILON DERIVATIVES, PROCESSES FOR THEIR PRODUCTION AND THEIR USE

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231
Attn: US/DO/EO

S I R:

Preliminary to examination of the above-identified application kindly amend the application as follows:

In the Claims:

In claim 6, lines 1-2, kindly delete "any of the preceding claims" and substitute therefor --claim 1--;

In claim 7, line 1, kindly delete "any of claims 4 to 6" and substitute therefor --claim 4--;

In claim 8, line 1, kindly delete "any of claims 4 to 7" and substitute therefor --claim 4--;

In claim 9, lines 4-5, kindly delete "any of the preceding claims" and substitute therefor --claim 1--;

In claim 10, line 4, kindly delete "any of the preceding claims" and substitute therefor --claim 1--;

In claim 11, line 4, kindly delete "any of the preceding claims" and substitute therefor --claim 1--;

In claim 12, line 4, kindly delete "any of the preceding claims" and substitute therefor --claim 1--.

Kindly amend claim 14 as follows:

14. (Amended) Process for the production of a compound of formula (6), characterized in that it comprises the process steps as disclosed in [claims] claim 9[, 10, 11 or 12 and 13, wherein the residues are defined as in the preceding claims].

In claim 15, line 2, kindly delete "claims 1 to 8" and substitute therefor --claim 1--;

In claim 17, line 3, kindly delete "claims 1 to 8" and substitute therefor --claim 1--.

REMARKS

The claims (as amended during Chapter II) of the above-identified application have been amended to remove all multiple dependencies. No new matter has been added. Accordingly, an early examination of the application is respectfully requested.

Respectfully submitted,

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Registration No. 28,988

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PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) **Internationale Patentklassifikation** 6 :
C07F 5/02, C07D 493/04, A61K 31/425, 31/365, A01N 43/90 // (C07D 493/04, 313:00, 303:00)

A3

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198 20 599.6 8. Mai 1998 (08.05.98) DE

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(81) **Bestimmungsstaaten:** AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(88) **Veröffentlichungsdatum des internationalen Recherchenberichts:** 13. Januar 2000 (13.01.00)

(54) **Title:** EPOTHILONE DERIVATIVES, A METHOD FOR THE PRODUCTION THEREOF, AND THEIR USE

(54) **Bezeichnung:** EPITHILONDERIVATE, VERFAHREN ZU DEREN HERSTELLUNG UND DEREN VERWENDUNG

(57) **Abstract**

The invention relates to epothilone derivatives, a method for the production thereof, and to their use for producing medicaments and plant protection products.

(57) **Zusammenfassung**

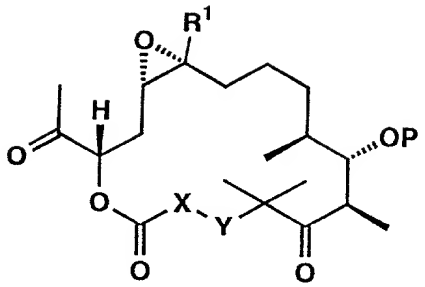
Die vorliegende Erfindung betrifft Epothilonderivate, Verfahren zu deren Herstellung und deren Verwendung zur Herstellung von Arzneimitteln und Pflanzenschutzmitteln.

4th May 1999/pl

Our ref: 9926 GBF
New International Patent Application
Gesellschaft für Biotechnologische Forschung mbH (GBF)

Epothilon derivatives, processes for their production and their use

The present invention relates generally to epothilon derivatives, to processes for their production and to their use in the manufacture of medicaments and plant protection agents. The invention relates especially to epothilon derivatives of the general formulae 2 to 6 shown below and to their use as medicaments and plant protection agents.



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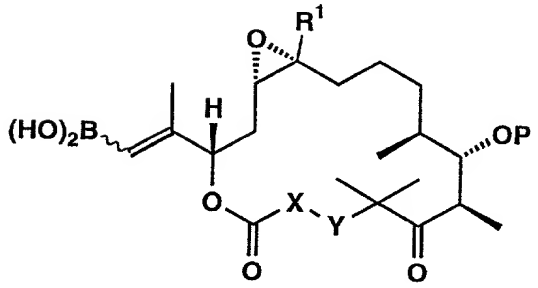

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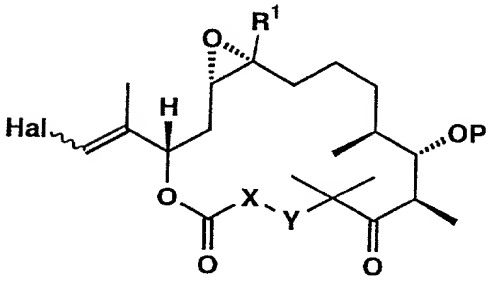

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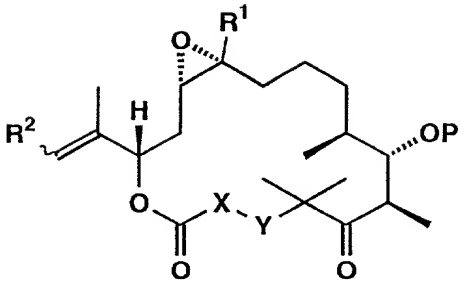

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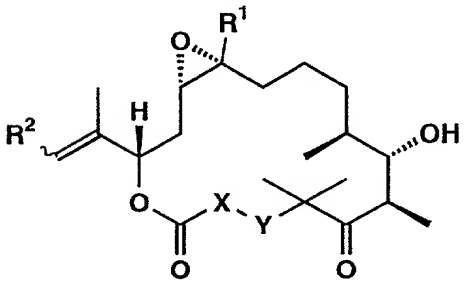

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In the above formulae:

R^1 = a H atom or a C_1- to C_8-alkyl group, preferably a C_1- to C_6-alkyl group, especially preferably a C_1- to C_4-alkyl group, especially a methyl, ethyl, propyl or butyl group,

R^2 = a monocyclic aromatic group, such as a 5- or 6-membered aromatic group (such as a phenyl ring) or a vinyl group, each of which may be substituted in the ortho- and/or meta- and/or para-position(s) by one, two, three, four or five, especially one or two, halogen atoms and/or OR^4 and/or NR^5R^6 groups and/or alkyl and/or alkenyl and/or alkynyl groups, wherein R^4, R^5 and R^6 each independently of the others have the same meanings as R^1, but are independent of R^1, or

R^2 = a monocyclic 5- or 6-membered heteroaromatic group which may have one or more, especially one or two, O and/or N and/or S atoms in the ring and/or may have OR^4 and/or NR^5R^6 groups and/or alkyl and/or alkenyl and/or alkynyl groups as substituents, wherein R^4, R^5 and R^6 are as defined above. In the definition of R^2 there are especially preferred C_1-C_6-alkyl or C_2-C_6-alkenyl and -alkynyl groups, especially C_1-C_4-alkyl or C_2-C_4-alkenyl and -alkynyl groups. As alkyl groups there are especially preferred methyl, ethyl, propyl and butyl groups and as heteroaromatic groups 6-membered heteroaromatic groups,

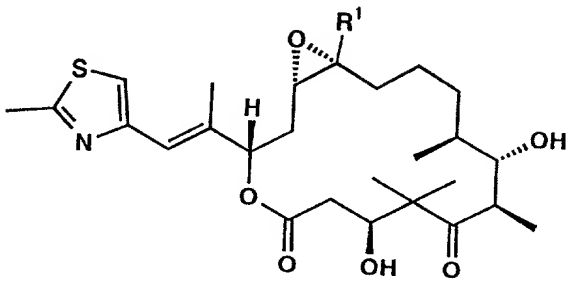
Hal = a halogen atom, such as Br or I,

X-Y = a group of the formula $-CH_2CH-OP$ or -CH=CH-, and

P = a protecting group, such as TMS.

The compounds according to the invention may be produced as follows:

Compounds of the formula (2) may be produced by reacting compounds of the formula (1)



as described in DE 195 42 986, the radicals being as defined above. In that reaction, especially the following conditions (i), (iii) and optionally (after (i)) also (ii) may be used:

(i) (a) O_3 in a solvent, such as CH_2Cl_2, and
(b) reductive working-up, for example with Me_2S;
(ii) (a) $(CH_3CO)_2O$, HCO_2H, NEt_3, DMAP;
(b) DBU; and
(c) MeOH, NH_3; and
(iii) Me_3SiCl, NEt_3.

Compounds of the formula (3) are obtainable by reacting a compound of the formula (2) with a compound of the formula $HC[B(OR)_2]_3$, such as tris(ethylenedioxyboryl)methane; R may be an alkyl or alkenyl group as defined above.

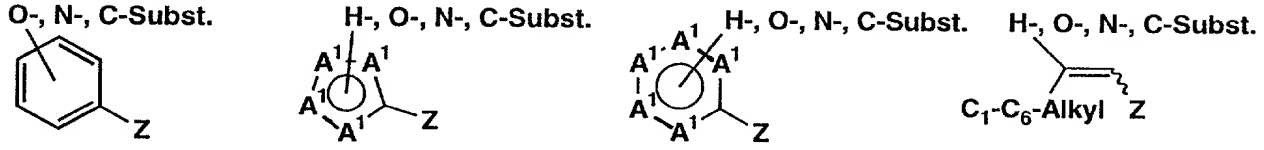
In the reaction there is optionally used a strong base, such as a C_1-C_4-alkyl-Li compound (such as butyllithium) or a di-C_1-C_4-alkylamine-Li compound (such as a dimethylamine-lithium compound). The reaction is generally carried out at low temperatures, such as, for example, at temperatures of

less than -30°C, preferably at temperatures of less than -50°C, especially preferably at temperatures of at least -78°C. Further reaction conditions may be found in D. Schummer, G. Höfle in *Tetrahedron* **1995**, *51*, 11219.

For example, a compound of the formula (2) is reacted with tris(ethylenedioxyboryl)methane and butyllithium at -78°C to form a compound of the formula (3).

A compound of the formula (4) may be produced from a compound of the formula (3) by reaction with N-iodo- or N-bromo-succinimide, optionally in a polar solvent, such as acetonitrile. Further reaction conditions may be found in the following literature reference: N.A. Petasis, I.A. Zavialor, *Tetrahedron Lett.* **1996**, 37, 567.

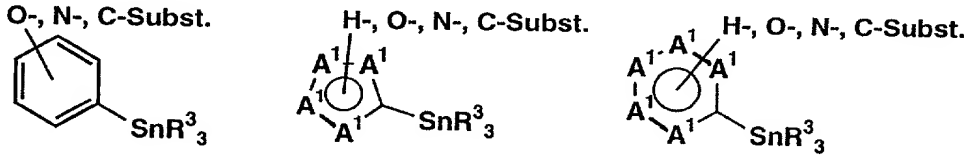
For the production of a compound of the formula (5), a compound of the formula (3) may be reacted within the framework of a Suzuki coupling with a compound of the formula R^2-Z, wherein R^2 has the meanings given above and Z may be a halogen atom or a group of the formula $-OSO_2CF_3$, -CH=CHI, $-CH=CHOSO_2CF_3$. The group R^2-Z may especially have the following structures:



wherein A^1 represents O, S, N or C atoms and the substituents O-, N- and C- correspond to the above-described groups OR^4, NR^5R^6 and alkyl, alkenyl and/or alkynyl groups.

Especially preferred as substituents "C" are C_1-C_6-alkyl or C_2-C_6-alkenyl and/or -alkynyl groups, especially C_1-C_4-alkyl or C_2-C_4-alkenyl and/or -alkynyl groups. As alkyl groups there are especially preferred methyl, ethyl, propyl and butyl groups.

Alternatively, a compound of the formula (5) may be produced by reacting a compound of the formula (4) by means of a Stille coupling with R^2-SnR^3_3, wherein R^2 is as defined above and R^3 is a C_1- to C_6-alkyl group, preferably a C_1- to C_4-alkyl group and especially preferably a methyl, ethyl, propyl or butyl group. In addition, the compound R^2-SnR^3_3 may have one of the following structures:



wherein the radicals and substituents are as defined above.

Furthermore, according to the invention, a compound of the formula (6) may be produced by removing the protecting group from the compound of the formula (5), for example with a weak acid, such as citric acid, or compounds such as TBAF, pyridine x HF. Optionally an alcohol, such as methanol, may be used as solvent, the temperature preferably being adjusted to values of, for example, from 40 to 60°C, preferably about 50°C.

In summary, the compound of the formula (6) may be produced by the above-described steps (epothilon A or B → (2) → (3) → (4) → (5) → (6) or epothilon A or B → (2) → (3) → (5) → (6)).

According to the invention there are also disclosed medicaments that contain at least one of the compounds (2), (3), (4), (5) or (6) and optionally customary carriers, diluents and adjuvants.

Such compounds may especially be used also as cytostatic agents and for plant protection in agriculture and/or forestry and/or in horticulture, the compounds optionally being used together with one or more customary carriers, adjuvants and/or diluents.

Examples

Synthesis of the ketone derivatives 2

For a detailed description see DE 195 42 986 A1.

Synthesis of the alkenylboronic acid derivatives 3

(see also D. Schummer, G. Höfle, *Tetrahedron* **1995**, *51*, 11219)

Typical Example (R^1 = H, X-Y = $CH_2CHOTMS$):

A solution of tris(ethylenedioxyboryl)methane (0.30 g, 1.5 mmol) in CH_2Cl_2/THF (1:1; 4 ml) was prepared and cooled under inert gas to -78°C. At that temperature, butyllithium (1.6M solution in hexane; 0.73 ml, 1.2 mmol) was added drop-

wise in the course of 10 minutes. After 2 hours, ketone 2 (81 mg, 0.15 mmol) in CH_2Cl_2/THF (1:1, 2 ml) was added, heated to room temperature and stirred for 17 hours. After the addition of MeOH (2 ml), the clear reaction solution was purified by means of preparative HPLC (Lichroprep RP-18, CH_3CN/H_2O 75 : 25). 57 mg (65 %) of alkenylboronic acid 3 were obtained in the form of an E/Z-isomeric mixture (6 : 4).

Selected typical data: LC-MS (ESI-MS): 585 (M^+ + H); ^{1}H-NMR: (300 MHz, CD_3OD): E-isomer: 1.91 (S, 3H), 5.16 (d, 1H, 10 Hz), 5.49 (s, 1H), Z-isomer; 1.85 (d, 3H, 1.1 Hz), 4.93 (s, 1H), 5.26 (d, 1H, 9.6 Hz).

Synthesis of the iodovinyl derivatives 4

(see also N.A. Petasis, I.A. Zavialor, *Tetrahedron Lett.* **1996**, *37*, 567)

Typical Example (R^1 = H, X-Y = $CH_2CHOTMS$):

At room temperature, N-iodosuccinimide (6.0 mg, 27 µmol) was added under inert gas and with the exclusion of light to a solution of alkenylboronic acid 3 (12 mg, 21 µmol; *E/Z 9:1*) in CH_3CN (150 µl) and stirred for 3 hours. After concentration, the residue was purified by means of preparative thin-layer chromatography (SiO_2, CH_2Cl_2/MeOH 95 : 5). 9 mg (66 %) of the iodovinyl derivative 4 were isolated in the form of an E/Z-isomeric mixture (9:1).

Selected typical data: LC-MS (ESI-MS): 667 (M^+ + H); ^{1}H-NMR: (300 MHz, $CDCl_3$); E-isomer: 1.82 (d, 3H, 1.1 Hz), 5.36 (d, 1H, 11 Hz), 6.43 (s, 1H), Z-isomer: 1.84 (d, 3H, 1.1 Hz), 5.54 (d, 1H, 10.5 Hz), 6.09 (s, 1H).

Suzuki coupling of the alkenylboronic acid 3

(see also A. Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178; A. Torrado, S. Lopez, R. Alvarez, A.R. De Lera *Synthesis*, **1995**, 285)

Typical Example (R^1 = H, X-Y = $CH_2CHOTMS$, R^2 = Ph):

A solution of alkenylboronic acid 3 (12 mg, 21 µmol; E/Z 2 : 8) and thallium ethanolate (2M solution in EtOH; 12 µl, 24 µmol) in THF (150 µl) was stirred at room temperature for 15 minutes, then a solution of phenyl iodide (4.0 µl, 6.0 mg, 29 µmol) and tetrakis(triphenylphosphino)-palladium (7.1 mg, 6.2 µmol) in THF (150 µl) was added dropwise in 30 minutes and again stirred for 30 minutes. After purification by means of preparative thin-layer chromatography (SiO_2, CH_2Cl_2/Et_2O 95 : 5) the phenyl-analogous epothilon 5 (10 mg, 79 %, E/Z 2 : 8) was obtained in the form of a colourless solid.

Selected typical data: LC-MS (ESI-MS): 617 (M^+ + H); ^{1}H-NMR: (300 MHz, $CDCl_3$): E-isomer: 1.87 (d, 3H, 1.4 Hz), 5.35 (d, 1H, 10.7 Hz), 6.54 (s, 1H), Z-isomer: 1.80 (d, 3H, 1.5 Hz), 5.61 (d, 1H, 10.2 Hz), 6.41 (s, 1H).

Stille coupling of the iodovinyl derivatives 4

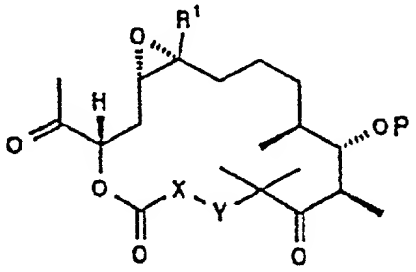
(see also K.C. Nicolaou, Y. He, F. Roschangar, N.P. King, D. Vourloumis, T. Li *Angew. Chem.* **1998**, *110*, (1/2), 89)

PCT Chapter II

International Patent Application PCT/EP 99/03 159
based on DE 198 20 599.6
Hoefle et al.; Epothilone derivatives etc.

Patent Claims

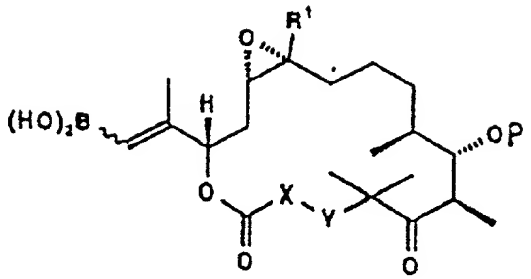
1. Epothilone derivative of formula (2)



wherein R^1 is a hydrogen atom or a C_{1-8}-alkyl group, X-Y is a group of formula $-CH_2CH-OP$ or $-CH=CH-$, and
P is a protective group, wherein
X-Y is excluded as group of formula $-CH_2CH-OP$ if R^1 means a hydrogen atom or a C_{1-4}-alkyl group.

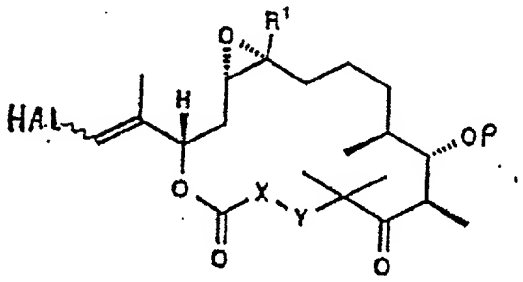
ART 34 AMDT

2. Epothilone derivative of formula (3)



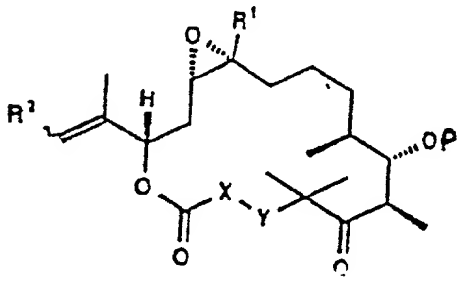
wherein the residues are as defined in claim 1.

3. Epothilone derivative of formula (4)



wherein the residues R^1, X-Y and P are defined as in claim 1, and Hal is a halogen atom such as Br or I.

4. Epothilone derivative of formula (5)

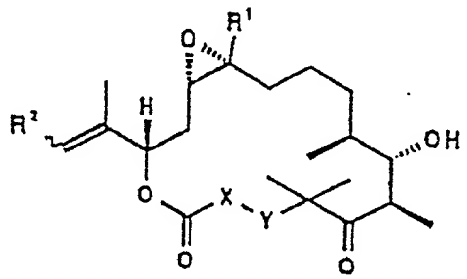


wherein the residues R^1, X-Y and P are defined as in claim 1, and R^2 is a monocyclic aromatic which can be substituted by a halogen atoms and/or OR^4- and/or NR^5R^6- and/or alkyl, alkenyl and/or alkinyl groups in ortho- and/or meta- and/or para-position, or a monocyclic 5- or 6-membered hetero aromatic, which can be provided with one or several O- and/or N- and/or S-atoms in the ring and/or which can be provided with OR^4- and/or NR^5R^6- and/or alkyl, alkenyl and/or alkinyl groups as substituents, wherein the residues R^4, R^5 and R^6 independently are defined as R^1 in claim 1, but are independent of R^1, wherein

(i) XY is excluded as group of formula -CH=CH- if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent and

(ii) X-Y is excluded as group of formula $-CH_2-CH-OP$ if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent.

5. Epothilone derivative of formula (6)



wherein the residues are defined as in claim 4 and, if X-Y means a group of formula $-CH_2CH-OP$, the protective group P has been removed, wherein

(i) XY is excluded as group of formula $-CH=CH-$ if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent and

(ii) X-Y is excluded as group of formula $-CH_2-CH-OP$ if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent.

6. Epothilone derivative according to any of the preceding claims, **characterized** in that R^1, R^4, R^5 and R^6 are a hydrogen atom or a C_{1-6}-alkyl group, especially a C_{1-6}-alkyl group.

7. Epothilone derivative according to any of claims 4 to 6, **characterized** in that the substituents of the monocyclic aromatic and/or hetero aromatic are C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkinyl groups, respectively, especially C_{1-4}-alkyl, C_{2-4}-alkenyl and C_{2-4}-akinyl groups, respectively and the halogen atoms fluoro, chloro, bromo or iodo atoms.

8. Epothilone derivatives according to any of claims 4 to 7, **characterized** in that the aromatic and hetero aromatic, respectively, is provided with 1, 2 or 3 substituents and the hetero aromatic is provided with 1, 2 or more and especially 1, 2, 3, or 4 hetero atoms.

9. Process for the production of a compound of formula (3),

characterized in that a compound of formula (2) is reacted with the compound of formula $HC[B(OR)_2]_3$ if wanted in the presence of a base, wherein the residues are defined as in any of the preceding claims and R is defined as R^1, but is independent of R^1.

10. Process for the production of a compound of formula (4), **characterized** in that a compound of formula (3) is reacted with N-iodo- or N-bromo succinimide and that the residues are defined as in any of the preceding claims.

11. Process for the production of a compound of formula (5), **characterized** in that a compound of formula (3) is reacted by a Suzuki coupling with a compound of formula R^2-Z , wherein R^2 is defined as in any of the preceding claims and Z can be a halogen atom or a group of formula $-OSO_2CF_3$, $-CH=CHI$, $-CH=CHOSO_2CF_3$.

12. Process for the production of a compound of formula (5), **characterized** in that a compound of formula (4) is reacted by a silent coupling (stille Kupplung) with R^2-SNR^3_3, wherein R^2 is defined as in any of the preceding claims and R^3 is a C_{1-6}-alkyl group, especially a C_{1-4}-alkyl group, preferably a methyl, ethyl, propyl or butyl group.

13. Process for the production of a compound of formula (6), **characterized** in that the protective group is removed from a compound of formula (5).

14. Process for the production of a compound of formula (6), **characterized** in that it comprises the process steps as disclosed in claims 9, 10, 11 or 12 and 13, wherein the residues are defined as in the preceding claims.

15. Therapeutical agent, containing at least one of the compounds described in claims 1 to 8 and optionally usual carriers, diluents and/or auxiliary agents.

16. Therapeutical agent according to claim 15, **characterized** in that it is a cytostaticum.

17. Plant protecting agent in agriculture and/or forest culture and/or horticulture, containing at least one compound described in claims 1 to 8 and optionally usual carriers, diluents and/or auxiliary agents.

Abstract

The present invention relates to epothilon derivatives, processes for their production and their use in the manufacture of medicaments and plant protection agents.

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PTO/SB/01 (12-97)
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	2727-127
First Named Inventor	Gerhard Hoefle
COMPLETE IF KNOWN	
Application Number	09 /674,877
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"Epothilon Derivatives, Processes For Their Production and Their Use"

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 05/07/1999 as United States Application Number or PCT International Application Number PCT/EP99/03159 and was amended on (MM/DD/YYYY) _____ (if applicable).

USSN 09/674,877

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
198 20 599.6	Germany	05/08/1998	☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

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(July 1998)

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (If applicable)

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Joseph C. Sullivan	18,720	John F. Gulbin	33,180
Gerald Levy	24,419		
Ronald R. Santucci	28,988		
Ronald E. Brown	32,200		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle if any)	Family Name or Surname
Gerhard	Hoefle

Inventor's Signature	× Gerhard Höfle					Date	DEC 21 2000
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City		State		ZIP		Country	

☒ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 3 of 3

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
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Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])		**Family Name or Surname**					
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
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Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])		**Family Name or Surname**					
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
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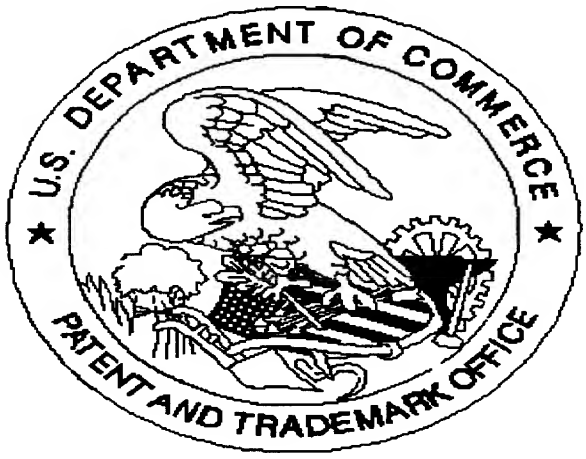

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